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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,353	05/30/2001	Yan Wang	020130-000111US	8319

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	**PAPER NUMBER**
1652	
MAIL DATE	**DELIVERY MODE**
11/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/870,353	WANG ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,17,22-30,32 and 34-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,17,22-30,32 and 34-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/5/2007 has been entered.

Applicants amendment of claims 15 and 30 and the cancellation of claims 20 and 33, in the paper of 10/26/2007, is acknowledged. Claims 15, 17, 22-30 and 32 and 34-42 are pending and at issue.

Applicants' arguments filed on 7/5/2007, have been fully considered and are not deemed to be persuasive to overcome the rejections previously applied. Upon further consideration a number of references not previously made of record have been included in the rejection. It is for this reason that prosecution is hereby re-opened. Any inconvenience to applicant is regretted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 17, 20, 22-30 and 32-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein comprising two heterologous domains wherein the first domain is a sequence-non-specific-double-stranded nucleic–acid-binding domain joined to a second domain which is a DNA polymerase domain, wherein said sequence-non-specific-double-stranded nucleic–acid-binding domain is selected from the group consisting of Sso7d or Sac7d, does not reasonably provide enablement for any protein comprising two heterologous domains wherein the first domain is a sequence-non-specific-double-stranded nucleic–acid-binding domain joined to a second domain which is a DNA polymerase domain, wherein said sequence-non-specific-double-stranded nucleic–acid-binding domain comprises an amino acid sequence that has at least 85% sequence identity to SEQ ID NO: 2 or said sequence-non-specific-double-stranded nucleic–acid-binding domain comprises an amino acid sequence that has at least 85% identity to the Sac7d sequence set forth in SEQ ID NO: 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 15, 17, 18, 20 and 22-42. In response to this rejection, applicants have amended claims 15 and 30 and the cancelled claims 20 and 33 and traverse the rejection as it applies to the newly amended claims.

Applicants continue to traverse this rejection as in their previous responses and note that applicants have amended claims 15 and 33 to recite at least 85% identity to a

reference sequence. Applicants further submit a declaration by one of the inventors, Dr. Yan Wang in which Dr. Wang discusses the previous references made of record. Applicants continue to submit that applicant's specification provides examples that show that both Sso7d and Sac7d increase processivity when joined to polymerases and directs the practitioner to the large body of art in this field that provides detailed structural insight into the interaction of Sso7d and Sac7d with DNA. Applicants continue to reference the Rule 132 Declaration by Dr. Peter Vander Horn and submit that the level of knowledge in this art is high and there is a large body of art in this field that provides detailed structural insight into the interaction of Sso7d protein with DNA.

Applicants submit that Dr. Wang's declaration explains that the experiments performed in the cited publications provide evidence that one of skill can successfully employ the extensive structural Sso7d/Sac7d data available in the art to predict the effects of sequence changes on Sso7d (or Sac7d) function. It continues to be noted that applicants continue to refer to the "function" of Sso7d and I continues to be emphasized that the function that is the more important to the enablement of the claimed invention, although certainly not solely important is not merely "DNA binding activity" but rather "enhanced processivity of the polymerase domain compared to the polymerase an identical protein that does not have the sequence non-specific double-stranded nucleic acid binding domain.

Applicants, based upon Dr. Wang's declaration, present applicants interpretation of the purpose, data, and conclusions drawn from each of the previous references cited, Wang et al. (Wang et al., Nucleic Acids Research, 2004, vol. 32, p 1197-1207), Shehi et

al. (Biochemistry, 2003, vol 42, pp. 8362-8) and Consonni et al. (Biochemistry, 1999, vol 38, pp 12709-17), which were presented in the previous office action, to evidence the unpredictability of the art with respect to the functional effect of altering specific residues of Sso7d. Applicants argue that rather than support the office's position of a lack of enablement of the claims, the references support the enablement of the claims,

Applicants complete argument is acknowledged, however, not found persuasive for the reasons previously stated and repeated below. It continues that the level of skill in the art is high, although applicants have not provided the guidance necessary to make the genus of proteins claimed, that encompasses those sequence non-specific double-stranded nucleic acid binding domains having a mere 85% sequence identity to the amino acid sequence of SEQ ID NO: 2.

As previously stated, the prior art teaches that single point mutations of Sso7d will affect the function of the nucleic acid binding domain and renders the art unpredictable. Applicant's own post filing art, Wang et al. (Wang et al., Nucleic Acids Research, 2004, vol. 32, p 1197-1207), teach the finding that mutational changes in Trp24 of Sso7d significantly reduce its effectiveness in enhancing processivity. Wang et al. further states that the use of a DNA binding protein with a much higher affinity for dsDNA could be detrimental to the catalytic activity of the polymerase and teach that further studies are needed to identify the optimal range of affinities of the dsDNA binding protein to achieve the ultimate balance between processivity and catalysis (page 1205, 1st full paragraph). Applicants submit that the studies of Wang et al. support applicants disclosure of the link between dsDNA binding activity and

processivity and applicants note that those mutants taught by Wang et al. while reducing dsDNA binding activity, did not completely destroy Sso7d function in enhancing processivity. While it is acknowledged that Wang et al. supports the association between dsDNA binding and the ability to increase the processivity of an associated polymerase, applicant's specification gives no guidance as to how the level of dsDNA binding relates to the increase in processivity. As was previously stated, Wang et al. teaches that the use of a DNA binding protein with a much higher affinity for dsDNA could be detrimental to the catalytic activity of the polymerase and teach that further studies are needed to identify the optimal range of affinities of the dsDNA binding protein to achieve the ultimate balance between processivity and catalysis. Thus based upon Wang et al. it is clear that while any associated increase in polymerase processivity is associated with dsDNA binding activity, applicants have not shown guidance as to how these are related, beyond the fact that they are related.

As previously stated, Shehi et al. (Biochemistry, 2003, vol 42, pp. 8362-8) teach the deletion of Glu53 in Sso7d could not be isolated and suggests that this mutation misfolds the protein and deletion Leu54 in Sso7d has limited solubility in aqueous solution (page 8364, 2nd column, 1st full paragraph). Both mutations demonstrate the unpredictability of the effect of point mutations in Sso7d on any particular function or attribute of Sso7d.

Applicants submit that Shehi et al. investigated the function of the C-terminus of Sso7d and created the Leu54 truncation in order to investigate the role of the C-terminal α-helix on stability and DNA binding activity. Dr. Wang submits that this region does not

contact the DNA in the structural analysis of Sso7d and Sac7d DNA binding interactions and that the L54delta mutant showed a similar association constant for binding to double stranded DNA as that of Sso7d, thus showing that such a mutation did not result in a loss of DNA binding activity.

While the above is acknowledged, this continues to support the earlier drawn conclusions that a single mutation may result in phenotypic alterations at various levels. Such effects may be seen at the most basic structural level, effecting the folding of the protein and its structural formation, and this may or may not also affect any of the various functions of the protein, such as dsDNA binding activity. Further still such mutations may and relationships may also relate to other such functions such as the ability to increase processivity of an associated polymerase. This is the structural to functional relationship of the ability to increase the processivity of an associated polymerase that additional guidance is necessary.

As also stated previously, Consonni et al. (Biochemistry, 1999, vol 38, pp 12709-17) teach the mutation of F31A and W23A in Sso7d impairs the capacity of the protein to bind dsDNA.

Applicants submit that Consonni et al. describes the solution structure of the Sso7d mutant protein F31A, in which this mutant was selected on the basis that it resulted in the alteration of a core hydrophobic residue that would be expected to be important for stability. Applicants further point out that this residue is highly conserved in other Sso7 family members. Dr Wang and applicants submit that on the basis of the type of mutation created and where it occurs in the protein that such an alteration in the

stability of the protein is not unexpected. Applicants comments and analysis of the results and analysis of Consonni et al. are appreciated, however, it continues that the art does not support applicants argued relationship between the structure of the protein and its ability to increase the processivity of an associated polymerase.

As was previously stated and repeated above, while the art teaches an association between dsDNA binding activity and the ability to increase the processivity of an associated polymerase polypeptide, such guidance is not specific beyond the fact that this relationship exists. It continues that a DNA binding protein with a much higher affinity for dsDNA could be detrimental to the catalytic activity of the polymerase and teach that further studies are needed to identify the optimal range of affinities of the dsDNA binding protein to achieve the ultimate balance between processivity and catalysis. Applicants in their analysis have not addressed this relationship between dsDNA binding activity and processivity such that applicants have enabled those proteins having a mere 85% identity to SEQ ID NO: 2.

It continues that the art teaches that sequence similarity alone does not necessarily provide a predictable correlation between the structure and specific function of a protein and applicant's arguments have not addressed the specific function that is the basis of the claims enablement issue. Neither the art nor the specification teach what other domains, regions, or specific amino acids of Sso7d are responsible for sequence non-specific dsDNA binding or more importantly enhancing processivity of an attached polymerase. The prior art supports the unpredictability of this area of technology.

Applicants limited guidance in light of the state and unpredictability of the art leads to the lack of enablement of the claimed genus. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any protein comprising two heterologous domains wherein the first domain is a sequence-non-specific-double-stranded nucleic–acid-binding domain joined to a second domain which is a DNA polymerase domain, wherein said sequence-non-specific-double-stranded nucleic–acid-binding domain comprises an amino acid sequence that has at least 85% sequence identity to SEQ ID NO: 2 or said sequence-non-specific-double-stranded nucleic–acid-binding domain comprises an amino acid sequence that has at least 85% identity to the Sac7d sequence set forth in SEQ ID NO: 10. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of thos proteins having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 6:30 am-3:00 pm, M--F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

rgh
10/26/2007

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER